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(54) Title: GLUCOSE CONTROL MATERIAL FOR TEST STRIPS

(57) Abstract

A non-serum based control reagent is disclosed which is useful for validating devices such as test strips for determining glucose. The reagent composition contains water, a predetermined amount of glucose, and a clay mineral. An especially preferred clay mineral is hectorite. A method of making the control reagent is also disclosed.

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GLUCOSE CONTROL MATERIAL FOR TEST STRIPS

BACKGROUND

The present invention relates to control material useful in validating testing devices such as test strips and dipsticks. More particularly, the present invention relates to a non-serum based, aqueous glucose control material and to a method for making said control material.

The field of clinical chemistry and clinical analysis is concerned, *inter alia*, with the determination and quantification of various substances in body fluids. Many examples of the substances which are determined can be given, and these include cholesterol, urea, cations, and glucose. These examples of analytes, as well as others, are assayed in diverse body fluids such as urine and blood.

The monitoring of the level of glucose in blood is important to the management of diabetes. The level of glucose in the blood is controlled by the amount of carbohydrate ingested and by insulin. Too much insulin lowers the glucose level, and too little will result in an abnormally high level of glucose. Both circumstances lead to serious health problems for the diabetic.

Most of the glucose testing done outside of the hospital laboratory is done in non-laboratory settings such as nurses' stations, physicians' offices and at

home. Testing is frequently done by measuring the amount of glucose in urine. As the level of glucose rises in the blood, it exceeds the ability of the kidney to reabsorb it, and glucose is excreted into the urine.

Although measurement of glucose in urine is useful, measurement of glucose in blood provides a more accurate reflection of the condition of the subject. Urine glucose does not accurately reflect the level of glucose in the blood since the level of glucose in urine is determined by the level of glucose in the blood and the ability of the kidney to reabsorb the glucose. Therefore, the urine sample cannot tell the diabetic how low his glucose level is.

Dry reagent test strips, sometimes referred to as dipsticks, are widely used for detecting glucose in urine and blood. These devices are characterized by their simplicity of use. In general, such test strips comprise plastic strips provided at one end thereof with an absorbent paper portion which has been impregnated with reagents such as an enzyme system and a color indicator compound which produces or changes color to form a detectable signal when the test strip is contacted with the analyte being determined. This change in color can be measured by comparing the color formed on the strip with a standard color chart calibrated to various glucose concentrations. More recently, however, to more accurately control the level of glucose in blood,

instruments have been developed which measure the color change in a reflectance photometer and thereby produce quantitative results. Examples of reaction systems which measure glucose using reflectance measurements include oxidative reactions, such as the glucose oxidase/peroxidase method, and reductive reactions, such as the glucose oxidase/ferricyanide method. The latter method is described in detail in Freitag, U.S. Pat. No. 4,929,545, the content of which is herein incorporated by reference. Instruments have also been developed which determine glucose by means of electrochemical methods in which a change in current is measured.

It will be understood that clinical analysis of the type described herein requires that any testing system be extremely accurate. In particular, when automated systems and instruments are used, it is essential to ensure that the elements of the analysis are reliable and that the measurement taken is valid. It is for this purpose that control reagents are used.

Westgard and Klee, in Textbook of Clinical Chemistry, N.W. Tietz, Ed., 1986, p. 430, define "control material" as "a specimen, or solution, which is analyzed solely for quality control purposes and is not used for calibration purposes." This standard reference work goes on to describe some of the requisites of control materials as follows: "They need to be stable materials, available in aliquots or vials, that can be analyzed

periodically over a long time. There should be little vial-to-vial variation so that differences between repeated measurements can be attributed to the analytical method alone.".

The above-cited reference, at page 433, discusses how the matrix of the control material should be the same as the material being analyzed. To that end, modified human serum is discussed as one type of control material. Indeed, the art now recognizes the term "control serum" as referring to control material based upon serum. This terminology will be used herein and is different from the term "control reagent," which, as used hereafter, refers to a control material which is not based upon, and which does not contain, serum of any type.

As has been pointed out above, one of the criteria which control materials have to satisfy is stability. Control materials based upon serum, however, are inherently unstable due to the various components contained therein. Further, sera will vary from source to source, so uniformity from lot to lot cannot be guaranteed. Thus, it is sometimes desirable to have a control material based upon a non-serum or serum-free medium.

An example of a serum-free control medium, or "control reagent" as used herein, is described in U.S. Pat. No. 4,729,959, issued to Ryan, which is directed to "a stable glucose reference control." This control

contains glucose in a range of from about 40 to 500 mg/dl, together with fixed red blood cells, in an aqueous suspension. The range of glucose concentrations given are sufficient to cover just about all ranges of glucose found in, e.g., blood.

The Ryan '959 patent points to a problem with aqueous control reagents at column 1, lines 50-55. Briefly, erythrocytes impart a degree of viscosity to blood which is absent in water based systems. This problem was also recognized in U.S. Pat. No. 3,920,580 issued to Mast. This patent teaches that aqueous solutions had not been consistent, and that a lack of reproducibility was observed when dry reagent strips were used with such materials. Mast teaches that suitable reagents could be prepared by using an antidiffusing agent in combination with glucose and water. The antidiffusing agents taught by Mast include polyvinylpyrrolidone, polyvinyl alcohol, polyethylene glycol, dextran, and bovine serum albumin. Beneficial amounts are taught to be between about 3 and 35 percent of antidiffusing agent. The control solution may also include adjuvants to obtain a particular color or physical appearance, which include colored latex particles and water-insoluble lake dyes.

Terashima, in European Appl. No. 266,216, discloses control or calibration solutions containing a water-insoluble dispersed phase, which can be a solid polymer

or copolymer having a molecular weight of 10^5 to 10^6, a liquid phase, or an emulsion of natural polymers such as sodium alginate. Particle sizes taught are about 0.01 μm to about 10 μm, and amounts taught are 1 to 50 percent by weight, preferably 10 to 50 percent by weight.

Louderback, in U.S. Pat. No. 3,977,995, teaches a calibrating fluid for automated instruments for blood cell counting and hemoglobin determination comprising a solution of hemoglobin which contains latex particles. The latex particles have a particle size of from about 5 to 20 microns, approximately the size of leukocytes, and are employed in the calibrating fluid at a concentration of 8,000 to 22,000 particles per microliter.

Kennamer *et al.*, in U.S. Pat. No. 5,028,542, the content of which is herein incorporated by reference, describe a non-serum based, glucose measurement control reagent in which the viscosity agent polystyrene sulfonate is used.

It has now been found that a suitable glucose control reagent can be formed without using any of the organic, polymeric materials referred to in Mast and others in the art as required ingredients. Rather, by combining an inorganic, non-polymeric clay mineral with a predetermined amount of glucose and water, along with additional optional materials, a suitable glucose control reagent can be made.

SUMMARY OF THE INVENTION

The present invention is a non-serum based glucose control reagent which comprises a predetermined, known amount of glucose, water, and an inorganic clay mineral. Preferred clay minerals are selected from the smectite group of clays, and an especially preferred clay is hectorite. The preferred concentration for the clay mineral is between about 0.1 and 1 percent by weight. It was found, quite unexpectedly, that the composition of the present invention is useful in validating testing devices such as test strips for the measurement of glucose. Further, it was surprisingly discovered that the control reagent of the invention is useful with a variety of types of glucose testing devices, including those devices employing oxidative glucose measurement methods, devices employing reductive glucose measurement methods, and also with devices utilizing electrochemical methods for determining glucose. Additional materials such as a buffer, a preservative, or a surfactant, either alone or in various additive combinations, may be mixed with the three required components. Another aspect of the present invention is a method for making the control reagent by mixing the glucose, water, and the clay mineral together.

A preferred clay mineral used in the invention is selected from the smectite, or montmorillonite, group of clays, which includes montmorillonite, beidellite,

nontronite, hectorite, saponite and sauconite. Less common smectite clays include volkhonskoite, medmonite and pimelite. An especially preferred clay mineral is hectorite. Smectites are crystalline clay minerals that carry a lattice charge and characteristically expand when solvated with water and alcohols. Hectorite is preferably and conveniently used in the form of a rheological additive, a specially processed hectorite clay gellant with a fine particle size which makes it readily dispersible in aqueous systems using conventional high speed dispersers. Wet particles should be fine enough to pass through a No. 200 sieve and thus less than about 75 μm in size. Clay minerals from other groups such as kaolinite and attapulgite clays are also within the scope and spirit of the present invention. In general, the clay chosen must be in a purified form free from grit, very fine-grained, and dispersible in liquid.

Essential to the invention are a predetermined amount of glucose, water, and the recited clay mineral. The water is used, of course, to create a reagent solution in which the clay particles are suspended. By "predetermined" is meant that, prior to formulation of the actual reagent, a concentration of glucose has been selected. This concentration may vary, as those skilled in the art will recognize. As has been mentioned above, the art recognized, *e.g.*, a range of from 40 to 500 mg/dl, but one may envision lower ranges to, *e.g.*, about

20 mg/dl. Some typical ranges would be from about 60 to about 240 mg/dl, or from about 60 to about 300 mg/dl.

The essential features of the invention, when the reagent is in the form of a dispersion or solution, are the solvent (water), the predetermined amount of glucose, and the clay mineral. The clay mineral may be present in, *e.g.*, a range of about 0.1 to about 1 percent by weight of the reagent. The weight percent of the clay mineral will be determined by the final reagent viscosity desired and the desired diffusion or permeability characteristics of the control material with the particular testing device with which it is to be used. Such characteristics will vary according to the particular clay chosen and its specific properties, which include the predominant content of the clay mineral, which is typically a hydrated silicate of aluminum, iron, or magnesium, the fineness of individual clay particles, which may be of colloidal size in at least one dimension, rheological properties, and the property of thixotropy in various degrees of complexity. Of course, the particular clay selected should also be one whose reactivity does not adversely interfere with the determination of glucose. It is not necessary that the control material have the same viscosity as whole blood; however, it is desirable that the permeability of the material, *i.e.*, the diffusion rate of the analyte, through the reagent matrix of the test strip approximate that of whole blood.

Optional additional components of the control material include typical additives such as buffers, preservatives, and surfactants. The art is replete with specific examples of suitable and useful additives for control material, and the skilled artisan will be able to determine useful amounts from a review of the art.

It may also be desirable to include a colored or colorable substance in the reagent mixture. This can be desirable because body fluid samples frequently possess a particular color as one of their properties. As the control reagent is being used to calibrate per a body fluid sample, it can be useful to calibrate against conditions as similar to the tested fluid as possible, including color.

BRIEF DESCRIPTION OF THE DRAWING

The present invention will be better understood by reference to the following detailed description of the invention when considered in combination with the drawing that forms part of the specification, wherein:

Fig. 1 is a graph showing the percent reflectance of the control material of the present invention at varying levels of glucose.

DESCRIPTION OF PREFERRED EMBODIMENTS

EXAMPLE 1

Preparation of Control Reagent

A preferred formulation of the control reagent of the present invention was prepared as follows: A 1 percent by weight aqueous dispersion of BENTONE® EW (Rheox, Inc., Hightstown, NJ) hectorite clay particles was prepared. It has been found that best results are obtained if the dispersion is made under high shear (minimum 3000 rpm) for at least 15 minutes using tepid water between pH 7 and 8. This is necessary to break up the hectorite platelets and thus ensure complete hydration of the particles and stabilization of viscosity. Although not an essential feature in the composition of the present invention, several biocides were also added, 0.30% by weight 2-phenoxyethanol, 0.30% by weight imidazolidinyl urea (available as GERMALL® 115, GAF Chemicals Corp.), and 0.15% by weight methylparaben. The dispersion then had glucose added to it in a predetermined amount, which was found to be 23 mg/dl as measured using a hexokinase reference method.

EXAMPLE 2

Efficacy of Control Reagent with Reductive Method

The control reagent described in Example 1 was then tested for its efficacy. As explained above, one of the most important features of a control reagent is its

consistency, meaning that values obtained using it should be fairly uniform from run to run.

With this in mind, the control reagent of Example 1 was applied to 5 different lots of test strips containing the glucose determination system described in U.S. Pat. No. 4,929,545. Briefly, this publication describes the determination of glucose using a reagent containing a glucose oxidase/ferricyanide/ferric compound system.

Ten replicates of each strip lot were measured using 10 different ACCU-CHEK® EASY instruments (Boehringer Mannheim Corp., Indianapolis, IN), and the mean glucose values and standard deviations were calculated. This procedure was then repeated using a commercially-available, non-serum based glucose control reagent, referred to herein as "Reference E". The results are set forth in Table 1 below.

Table 1

Strip Lot No.	Control	Mean	Std. Dev.
65c	1% Bentone	21.0	1.9
405	1% Bentone	39.1	5.2
406	1% Bentone	39.2	4.8
410	1% Bentone	37.4	6.0
420	1% Bentone	27.5	3.6
65c	Reference E		
405	Reference E	72.2	8.8
406	Reference E	69.5	6.8
410	Reference E	57.3	7.3
420	Reference E	52.5	11.0

The hexokinase-measured glucose level was 23 mg/dl for the 1% Bentone control and 19 mg/dl for the Reference E control material. These results show a level of

consistency well within that required of a control reagent, as is indicated by the comparative standard deviation values reported for each set of tests.

EXAMPLE 3

Efficacy of Control Reagent with Oxidative Method

A control reagent comprising a 1 percent aqueous dispersion of VAN GEL® ES (R.T. Vanderbilt Company, Inc., Norwalk, CT) clay particles was prepared using the following: 2.0 g Van Gel ES, 200.0 g deionized water, and 0.20 g PLURONIC® L-35 (polyoxyalkylene ether from BASF Corp.). To this was added 0.5 M MES/CAPS buffer to make 50 mM. The mixture was homogenized for 15 minutes. Eleven aliquots of this dispersion then had glucose added to them in predetermined amounts ranging from 26.0 to 429.0 mg/dl as measured using a hexokinase reference method.

Seven replicates of each control were then measured using bG® Test Strips (Boehringer Mannheim Corp., Indianapolis, IN), which utilize an oxidative glucose oxidase/peroxidase method, and seven different ACCU-CHEK II instruments. The percent reflectance readings (two reaction pads per strip) were recorded, and standard deviations and coefficients of variation were calculated. The results obtained are shown in Table 2 below.

Table 2

Glucose (mg/dl)	Mean (%R) bG3	Mean (%R) bG6	Std. Dev. bG3	Std. Dev. bG6	Coeff. Var. bG3	Coeff. Var. bG6
26	78.6	58.1	0.49	0.65	0.006	0.011
37	78.4	45.7	0.48	0.66	0.006	0.014
61	76.6	33.7	0.55	0.63	0.007	0.019
72	74.0	31.0	0.40	0.39	0.005	0.013
99	68.2	27.3	2.37	0.52	0.035	0.019
122	52.8	24.0	1.66	0.57	0.032	0.024
161	37.5	19.4	1.04	0.35	0.028	0.018
214	24.2	15.0	0.93	0.31	0.038	0.021
260	17.9	13.0	0.29	0.31	0.016	0.024
379	9.1	9.5	0.25	0.28	0.027	0.030
429	7.1	9.1	0.21	0.63	0.030	0.069

A dose response curve was also plotted, and this has been reproduced as Figure 1. These results obtained using an oxidative glucose measurement method also show a level of performance well within that required of a control reagent.

EXAMPLE 4

Efficacy of Control Reagent with Electrochemical Method

A 0.55 percent by weight aqueous dispersion of Bentone EW clay particles was prepared as described in Example 1. Several biocides were also added, 0.30% by weight 2-phenoxyethanol, 0.30% by weight Germall 115, and 0.15% by weight methylparaben. Thirteen aliquots of this dispersion then had glucose added to them in predetermined amounts ranging from 21.0 to 661.0 mg/dl as measured using a hexokinase reference method. One aliquot had no glucose added.

Using the electrochemical, amperometric biosensor method described in PCT Application No. PCT/US90/07374, ten replicates of each control were then measured, and the current readings at 10 seconds were recorded. Standard deviations and coefficients of variation were calculated, and these were compared with values obtained using capillary blood samples having glucose levels ranging from 1.3 to 787.8 mg/dl. The results obtained are shown in Table 3 below.

Table 3

Glucose (mg/dl)	Control	Mean (µamps)	Std. Dev.	Coeff. of Var.
0.0	.55% Bentone	1.51	0.08	5.05
21.0	.55% Bentone	4.23	0.15	3.48
30.0	.55% Bentone	5.42	0.11	1.99
39.0	.55% Bentone	6.44	0.21	3.34
42.0	.55% Bentone	7.93	0.27	3.38
58.0	.55% Bentone	9.21	0.31	3.33
64.0	.55% Bentone	9.62	0.36	3.77
86.0	.55% Bentone	12.50	0.34	2.74
95.0	.55% Bentone	14.04	0.29	2.04
115.0	.55% Bentone	17.69	0.25	1.39
129.0	.55% Bentone	19.71	0.42	2.11
228.0	.55% Bentone	32.77	2.20	6.71
439.0	.55% Bentone	52.70	3.26	6.19
661.0	.55% Bentone	68.98	7.18	10.41
1.3	blood sample	1.60	0.12	7.33
21.0	blood sample	3.34	0.10	2.88
42.5	blood sample	6.16	0.18	2.86
83.5	blood sample	12.44	0.23	1.83
123.3	blood sample	18.48	0.32	1.71
301.0	blood sample	45.33	1.00	2.20
451.0	blood sample	67.44	1.54	2.28
599.0	blood sample	88.79	1.90	2.14
787.8	blood sample	111.91	8.14	7.27

These results show a level of consistency well within that required of a control reagent, as is indicated by the comparative standard deviation values

and coefficients of variation reported for each set of tests.

It will be understood that the specification and examples are illustrative but not limitative of the present invention, and that other embodiments within the spirit and scope of the invention will suggest themselves to those skilled in the art.

What is claimed is:

1. A serum-free control reagent for glucose determination comprising a mixture of a predetermined amount of glucose, water, and a clay mineral.

2. The control reagent of claim 1, wherein said clay mineral is selected from the group consisting of montmorillonite, beidellite, nontronite, hectorite, saponite, and sauconite.

3. The control reagent of claim 1, wherein said clay mineral is hectorite.

4. The control reagent of claim 1, wherein said clay mineral is present in an amount ranging from about 0.1 to about 1.0 percent by weight of said control reagent.

5. The control reagent of claim 1, further comprising a buffer.

6. The control reagent of claim 1, further comprising a preservative.

7. The control reagent of claim 1, further comprising a surfactant.

8. The control reagent of claim 1, further comprising a colored or color-forming compound.

9. A process for making a serum-free control reagent for glucose determination comprising mixing a predetermined amount of glucose with water and a clay mineral.

10. The process of claim 9, wherein said clay mineral is selected from the group consisting of montmorillonite, beidellite, nontronite, hectorite, saponite, and sauconite.

11. The process of claim 9, wherein said clay mineral is hectorite.

12. The process of claim 9, wherein said clay mineral is present in an amount ranging from about 0.1 to about 1.0 percent by weight of said control reagent.

13. The process of claim 9, further comprising mixing a material selected from the group consisting of a buffer, a preservative, a surfactant, and a colored or color-forming compound with said predetermined amount of glucose, water, and clay mineral.

INTERNATIONAL SEARCH REPORT

Inter onal application No.
PCT/US94/13445

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :G01N 31/22, 33/48, 33/49, 33/50
US CL :436/8, 10, 12, 13, 14, 15, 16, 174, 183, 826; 435/14; 252/408.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 436/8, 10, 12, 13, 14, 15, 16, 174, 183, 826; 435/14; 252/408.1 -

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US, A, 4,826,535 (GODLY) 02 MAY 1989, column 3, lines 63-65 and column 4, example 1.	1, 2, 4-6, 8-10 and 12-13 --- 3 and 11
X	US, A, 3,950,349 (BUCKLEY ET AL) 13 April 1976, column 10, lines 63-68 and column 11, lines 4-6.	1, 4-6, 8, 9, and 12-13
X	US, A, 4,237,019 (SINGER ET AL) 02 December 1980, column 13, example 17.	1, 4, 6, 8-9, and 12-13
X	US, A, 4,291,497 (MANANKOV) 29 September 1981, column 7, lines 23-27.	1, 5, 9 and 13
Y	US, A, 5,028,542 (KENNAMER ET AL) 02 July 1991, column 2, example 1.	1-13

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
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"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 30 JANUARY 1995	Date of mailing of the international search report 01 MAR 1995
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Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

Int. ional application No.
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B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

APS
search terms: water, glucose, clay, hectorite, montmorillonite, beidellite, nontronite, saponite, sauconite, volkhonskoite, medmonite, pemilite, smectite, kaolinite, attapulgite